The interest of amyloid PET imaging in the diagnosis of Alzheimer's disease

Rik Vandenberghe[1,2,3], Katarzyna Adamczuk[1,3], Koen Van Laere[4]

[1]Laboratory for Cognitive Neurology, Department of Neurosciences, University of Leuven, [2]Neurology Department, University Hospitals Leuven, [3]Alzheimer Research Centre, University of Leuven, Leuven Institute for research into Neurodegenerative Disorders, University of Leuven, Belgium; Nuclear Medicine and Molecular Imaging, University Hospitals and University of Leuven, Belgium

Correspondence to: Rik Vandenberghe, M.D., Ph.D., Neurology Department, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium, e-mail: rik.vandenberghe@uz.kuleuven.ac.be, phone + 32 (0)16 344280, fax: + 32 (0)16 344285
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Abstract

Purpose of the review

To evaluate the potential clinical utility of amyloid imaging.

Recent findings

Amyloid PET is a valid in vivo marker of neuritic plaque load and correlates with amyloid plaque surface area. Abundant diffuse plaques, however, with scant neuritic plaques can also give rise to a positive scan, most often reported in association with Lewy body disease. Specificity of amyloid PET for discriminating AD from healthy controls is higher than that of structural MRI. Sensitivity for discriminating AD from healthy controls or from FTLD is also higher than that of fluorodeoxyglucose-PET, with higher interreader reliability. Within a same centre there is high concordance between dichomization of cases based on amyloid PET versus cerebrospinal fluid Aβ42. In a tentative algorithm, we restrict clinical-diagnostic use to dementia with age of onset before 60 years, primary progressive aphasia and corticobasal syndrome, cases with objective cognitive deficits that could be due to a neurodegenerative cause but also have significant cerebrovascular or psychiatric comorbidity, and rapidly progressive dementia.

Summary

Empirical studies how amyloid PET can change clinical-diagnostic thinking are starting to emerge. Key questions to be resolved are its role compared to cerebrospinal fluid markers and its impact on patient outcome.

Key words

amyloid PET, clinical utility, Alzheimer's disease

1 Introduction

Our confidence in the accuracy of a diagnosis of clinically probable Alzheimer's disease is mainly founded on clinicopathological series with the neuropathological diagnosis as standard-of-truth. A neuropathological diagnosis of Alzheimer's (AD) [1] relies on the amount of neuritic plaques in prespecified regions [2] and the topographical spread of neuritic and diffuse amyloid plaques [3] and neurofibrillary tangles [4]. In a multicenter academic memory clinic series, the positive predictive value of a diagnosis of clinically probable AD for the presence of a moderate to severe amount of neuritic amyloid plaques and neurofibrillary tangles fulfilling Braak stage 3-6 was 83%, with a sensitivity and specificity of 71% [5**]. Inversely, when the clinical premortem diagnosis was a non-AD dementia, more than one third nevertheless met or exceeded minimum threshold levels for AD histopathology [5**]. A diagnosis of possible AD had an even lower positive predictive value [5**]. Improving diagnostic accuracy is an important goal in possible AD, but clearly there remains room for diagnostic improvement in clinically probable AD too. Conceivably, our diagnostic accuracy at the time of diagnosis and during the initial years of follow-up will be even lower than what the neuropathological series suggests. The same goes for predementia compared to the dementia stage.

The goal of this review is to address whether and how amyloid positron emission tomography (PET) imaging can enhance early diagnostic accuracy of possible and probable AD. One of the first requirements for clinical utility of a novel diagnostic technique is that it either improves diagnostic accuracy over and above standard clinical procedures or (partly) replaces current diagnostic procedures with comparable accuracy in a cost-effective manner. The current review will focus principally on the gain in diagnostic accuracy that amyloid imaging may permit under well-defined circumstances in clinical practice. Empirical evidence on how this affects patient management and outcome is still limited at the moment. The importance of amyloid scanning in a clinical research context (e.g. therapeutic trials) is also beyond the scope of this review.

At the time of writing, only ^{18}F-florbetapir has received regulatory approval for clinical use for detection of neuritic plaque load in patients with objective cognitive deficits in whom a diagnosis of Alzheimer's disease is considered.

2 Consistency within and between amyloid imaging modalities

The amyloid PET tracers developed to date belong to various chemical classes. According to a postmortem study of homogenized brain tissue in AD and controls, thioflavine T derivatives (such as ^{11}C-Pittsburgh compound B (PIB) and its derivative ^{18}F-flutemetamol), stilbenes (^{18}F-florbetapir and ^{18}F-florbetaben, among others), and benzofuranes (^{18}F-NAV4694) share a common high-affinity binding site that explains most of the signal in AD [6**]. The majority of the currently available ^{18}F-ligands has been compared in vivo to ^{11}C-PIB (Table 1): Neocortical values for retention of ^{18}F-amyloid ligands correlate well with neocortical values of retention of ^{11}C-PIB. For ^{18}F-florbetapir [7, 8], the regression slope is less steep than for other ligands, suggesting a smaller dynamic range (Table 1). For the ^{18}F-ligands in general, correlation in subcortical white matter is much lower, and only NAV4694 has a high correlation value with ^{11}C-PIB also in white matter [9**] (Table 1).

Test-retest values (% difference between two time points divided by the average obtained at the two time points) of Standardized Uptake Value Ratios (SUVR) for a composite cortical volume of interest

	^{18}F-flutemetamol		^{18}F-florbetapir		^{18}F-florbetaben		^{18}F-NAV4694	
	r	m	r	m	r	m	r	m
Composite	0.91	0.99	0.78 0.86-0.95	0.33 0.59-0.64	0.97	0.71	0.99	0.95
Frontal	0.92	1.00	0.81	-	0.94-0.96	-	0.95-0.99	-
Parietal	0.92	1.01	0.58	-	0.94	-	0.97	-
Lateral temporal	0.91	0.99	0.68	-	0.96	-	0.99	-
Posterior cingulate	0.91	1.01	0.79	-	0.96	-	0.99	-
Anterior cingulate	0.88	0.91	0.81	-	0.94	-	0.98	-
Medial temporal	0.83	0.74	-	-	0.82	-	0.95	-
Occipital	0.89	1.03	-	-	0.92	-	0.96	-
Striatum	0.84	0.88	-	-	0.95	-	0.98	-
Subcortical white matter	0.22	0.36	-	-	0.63	-	0.79	-
Pons	0.63	0.50	0.38	-	0.50	-	0.87	-

Table 1: **Correlations between amyloid ligands.** Within-subject correlations between SUVR for ^{11}C-PIB and ^{18}F-flutemetamol (20 AD, 20 MCI) [10], ^{18}F-florbetapir (14 AD, 12 healthy controls) [7, 37], ^{18}F-florbetaben (10 AD, 10 MCI) [19], and ^{18}F-NAV4694 (7 AD, 10 MCI, 25 healthy controls, 3 FTLD patients) [9**]. *m*: region-wise linear slope; *r*: Pearson correlation coefficient; SUVR: Standardized Uptake Value Ratio; BP: Binding Potential; *Dash*: not reported.

with cerebellum as reference have been reported for ^{18}F-flutemetamol (1.5, S.D. 0.7) [10], ^{18}F-florbetapir (2.40, S.D. 1.41) [11], ^{18}F-florbetaben (6.2, range 0.6-12.2) [12] and ^{18}F-NAV4694 (7.5, S.D. 6.5) [13]. Fleisch' κ has been reported for ^{18}F-flutemetamol (0.86-0.96) [10, 14**]), ^{11}C-PIB (0.90) [15], ^{18}F-florbetapir (0.58-0.76) [11, 16**] and ^{18}F-florbetaben (0.60 [17]; 0.89-0.94 [18]). Cohen's effect sizes to discriminate AD from healthy controls vary from study to study, even for the same compounds, ranging between 1.3 and 3.8 [15, 17, 12, 19, 9**, 18]. So far no published studies are available that have directly compared performance between ^{18}F-amyloid ligands within the same subjects in vivo which would be highly informative for the clinician.

3 Validation against neuropathology

In a clinical context, generally nuclear medicine physicians will read the scans in terms of a positive, a negative or an indeterminate scan with regards to the presence of Aβ [20**]. Regions of known predilection of increased ligand retention that have a high diagnostic weight are the precuneus and posterior cingulate, lateral temporal cortex and orbitofrontal cortex, and also the ventral striatum [21*] (Fig. 1). Binary visual reads predict the presence of neuritic amyloid plaques with high sensitivity (96%) and specificity (100%) according to the ^{18}F-florbetapir phase 3 trial [22**]. Amyloid ligand retention correlates with immunohistochemical measures of amyloid plaque surface area [22**, 14**].

Academic clinicopathological case reports defined false-positives and false-negatives based on conventional neuropathological nosological diagnoses rather than a newly developed binarized neuritic plaque score [2, 4]. A positive ^{11}C-PIB scan can occur with a neuropathological diagnosis of Lewy-body disease rather than Alzheimer's disease when diffuse plaques are abundant (e.g. [23**]). This has also been described in one cognitively intact control [24*]. Two false-negative cases compared to conventional neuropathological standards have been reported [25**, 24*]. The prespecified regions sampled according to CERAD criteria do not fully coincide with

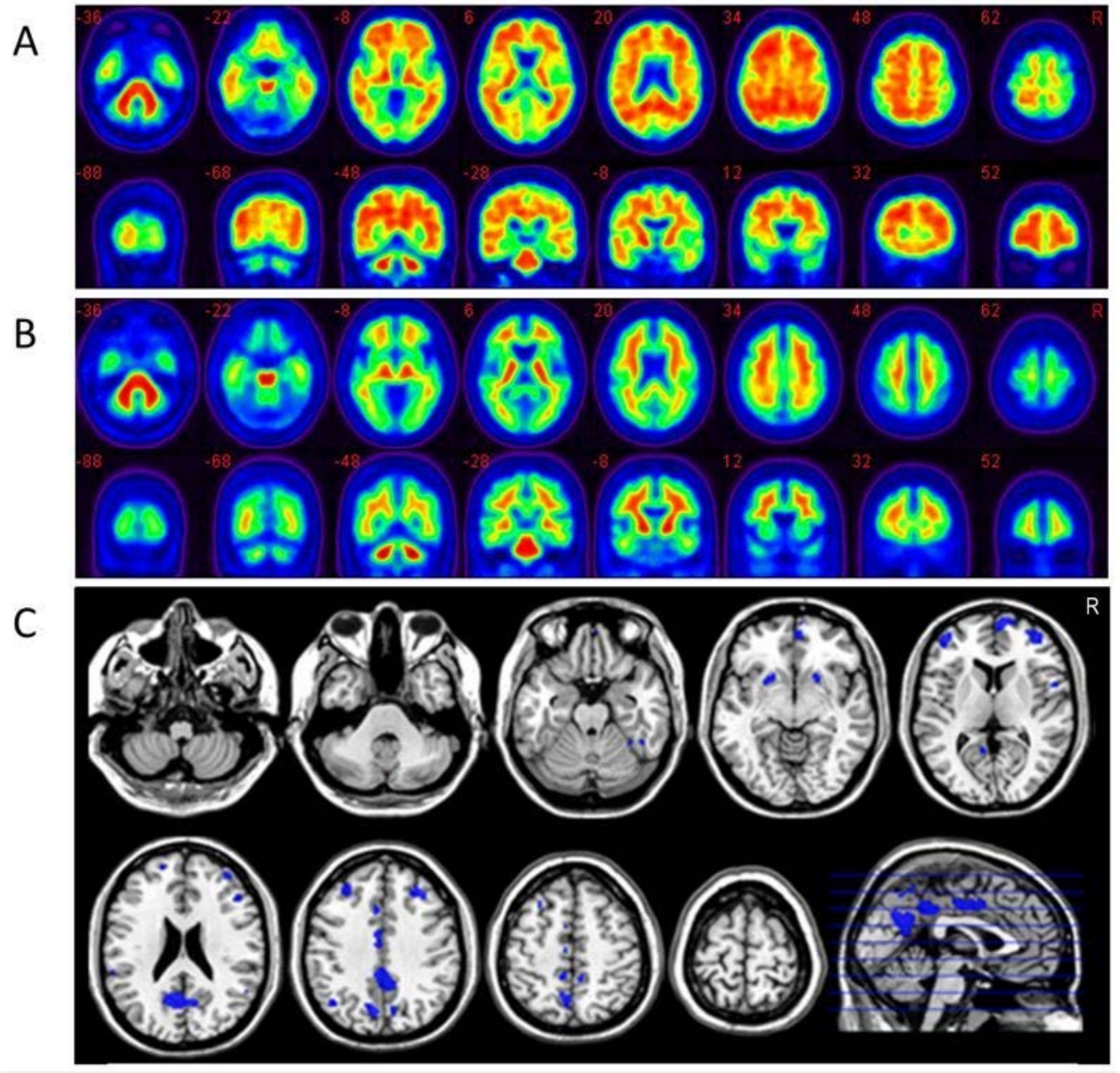

Figure 1: **Representative positive and negative scan. A.** ^{18}F-flutemetamol scan, obtained in a clinically probable AD case, with a positive visual read. **B.** ^{18}F-flutemetamol scan, obtained in a cognitively intact healthy volunteer, with a negative visual read. **C.** Voxels with the highest feature weight for discriminating between clinically probable AD and healthy controls.

the regions of predilection for increased amyloid ligand retention. Another explanation for a false-negative scan may be the occurrence of 'PIB-refractory' amyloid plaques for yet unknown reasons. A special instance of such refractoriness is AD due to the Arctic Amyloid Precursor Protein mutation [26]. Overall, given the high accuracy obtained in large-scale clinicopathological series, the occurrence of false-positives and false-negatives is probably a relatively rare event except for Lewy body cases exhibiting high amounts of diffuse plaques [23**].

4 Amyloid imaging versus other technical investigations in clinical use

In order to define the role of amyloid imaging in clinical practice, it is important to position it with respect to other technical investigations in clinical use and define to which degree it would replace these investigations or provide complementary information.

4.1 Amyloid imaging and structural MRI

The sensitivity for discriminating between clinically probable AD and controls is similar for amyloid PET and structural magnetic resonance imaging (MRI) according to a supervised machine learning analysis of the ^{18}F-flutemetamol phase 2 data [21*]. Specificity, however, is significantly lower for the MRI gray matter maps than for ^{18}F-flutemetamol PET (68% as opposed to 92%) [21*], probably because there is substantial overlap in hippocampal volume loss between normal aging and AD patients [27, 28**]. According to a population-based study (mean age 78 years), 40% of cognitively intact individuals show patterns of MRI volume loss or FDG hypometabolism corresponding to what is seen in Alzheimer's disease [29**]. Only 40% of these had an abnormal amyloid PET scan [29**, 30**].

4.2 Amyloid PET versus FDG PET

Visual readings of ^{11}C-PIB scans have a higher sensitivity and specificity than fluorodeoxyglucose-PET (FDG-PET) to discriminate clinically probable AD cases from healthy controls [34]. In the discrimination of clinically probable AD from clinically probable FTLD, accuracy is comparable, but ^{11}C-PIB has a higher sensitivity but specificity can be lower depending on the age range of included subjects [35]. Moreover, interrater agreement of the visual reads is higher for ^{11}C-PIB (Fleiss κ 0.96) than for FDG-PET (Fleiss κ 0.72) [35]. In atypical variants of AD (such as posterior cortical atrophy or the logopenic variant of AD), the topography of hypometabolism reflects the clinical phenotype while the distribution of amyloid ligand retention does not [31, 7, 32*], in accordance with what one would expect based on neuropathology [33**] (Fig. 2).

4.3 Amyloid imaging versus CSF

Dichotomization based on ^{11}C-PIB is highly concordant with that based on cerebrospinal fluid (CSF) Aβ_{42} [36]. When ^{18}F-florbetapir and CSF Aβ_{42}[37] were compared, discordance occurred more frequently [37]. The relative place of amyloid PET versus CSF Aβ42 in a diagnostic algorithm remains one of the questions to be resolved. An advantage of amyloid PET may be the high test-retest reliability and between-centre comparability of cut-offs and interpretation [38*] compared to CSF.

5 Changes in clinical-diagnostic thinking

According to a pioneering investigator-driven clinical utility study [39**] the referring clinician changed his/her diagnosis in 23% of cases following FDG- and amyloid PET combined, principally based on the amyloid PET findings, d emonstrating t he a dded d iagnostic v alue o f a myloid i maging i n a r ealistic s etting e ven w ithin a clinically highly experienced and dedicated Alzheimer centre [39**]. An industry-sponsored prospective study [40**] came to similar conclusions. Even in diagnostic trials where the binary read constitutes the primary study outcome, the proportion of false-positive clinical AD diagnosis at study entry has been high (37%) [16**]. Similar discrepancies between the clinical diagnosis at entry and the amyloid scan have been reported in therapeutic phase 3 trials evaluating amyloid-lowering drugs, in particular in APOEϵ4 noncarriers, and in the Alzheimer's Disease

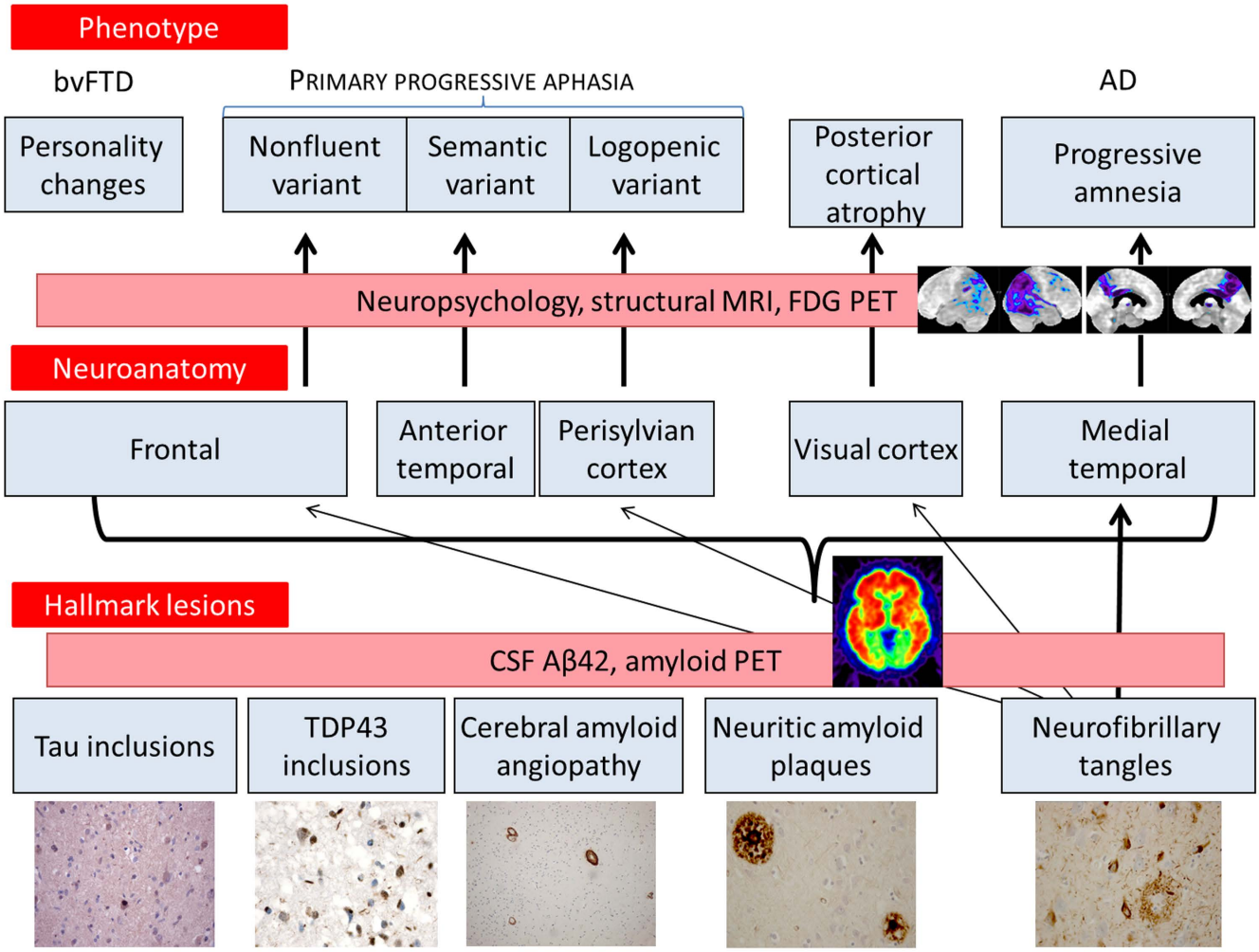

Figure 2: **Schematic view of how clinical phenotypes, lesion topography and neuropathological hallmark lesions relate to each other [44]**. The clinical phenotype stands in a relatively direct one-to-one relationship to the topography. In vivo measures that are situated at the level of the topographical distribution of the pathology are neuropsychology, structural MRI, and FDG-PET. However, the relationship between the topography and the underlying neuropathological hallmark lesions is probabilistic, meaning that the regional predilection of specific lesion types is a matter of probability, with significant inter-individual variation. Measures that are more closely related to the underlying neuropathological hallmark lesions are currently restricted to CSF measures of Aβ42 and phosphotau, and amyloid imaging. This is a schematic view, some neuropathological hallmark lesions are not shown such as Lewy bodies, and the relationship between the hallmark lesions and the topography is of a complexity that cannot be adequately summarized in this type of scheme.

Neuroimaging Initiative (ADNI) observational cohort, in which 77% of AD patients had a positive ^{18}F-florbetapir scan [41].

One of the main methodological caveats in industry-sponsored trials of clinical utility [42, 40**] is to avoid bias in favor of a positive study outcome due to the partially subjective evaluations by physicians in terms of pre- and post-scan diagnosis, impact on disease management or confidence rating and the relatively unblinded nature of the primary outcome evaluation in studies conducted until now [42, 40**].

6 Clinical scenarios encountered in a memory clinic in relationship to the potential utility of amyloid imaging or lack thereof

Schematically, one could envisage two radically different approaches: to apply amyloid imaging in a limited subset of patients who according to dementia experts fulfill well-delineated criteria, or, alternatively, to divulge the technique at the different healthcare levels where the diagnostic gain would be largest at those levels where diagnostic accuracy currently is lowest. The latter approach however has to take into account the relatively frequent occurrence of positive scans even in the absence of cognitive complaint [29**, 41, 43*]. In a healthcare system that wishes to provide equal access to state-of-the-art medical resources for all citizens, the first option, i.e. restricted use if clinical expert diagnosis and a conventional approach (e.g. using structural imaging) lack accuracy, would probably be the only affordable option. The main factors on which this judgment will be based are the a priori probability of AD prior to the scan and the value attached to the increase in diagnostic utility in the context of (currently limited) therapeutic options.

6.1 Age-dependence of the clinical utility of amyloid imaging

In early-onset dementia (defined here restrictively as dementia with onset below the age of 60), fronto-temporal lobar degeneration (FTLD) is as frequent as AD as a cause of dementia. Non-AD lesions that have a topographic distribution similar to Alzheimer's pathology may cause a clinical phenotype similar to the typical amnestic syndrome seen in clinically probable AD [44, 45**]. A diagnosis may have a significant impact at the personal and familial emotional and relational level as well as at the level of third-party payers. An accurate diagnosis may also guide the search for a genetic cause. Treatment options and clinical/behavioral progression to be expected over the disease course also differ between AD and FTLD. The prevalence of a positive amyloid scan below the age of 60 years in the absence of clinical symptoms is very low so that a positive scan is more likely to be related to the clinical symptoms compared to the older age group.

At the other end of the age spectrum, a third of cognitively intact subjects above the age of 78 [29**, 41] have a positive amyloid scan, and 50% above the age of 82 [43*]. As a consequence, the specificity in terms of a clinical disease diagnosis necessarily will be relatively lower in this age group. This does not mean that the positive scan is irrelevant: cognitively intact amyloid-positive subjects show more cognitve decline during up to 10 years preceding the scan than amyloid-negative subjects, even when matched for Apolipoprotein E ε4 status [46**].

6.2 Focal non-amnestic syndromes caused by neurodegenerative disease

In a memory clinic the focal non-amnestic syndromes mainly refer to primary progressive aphasia (with three variants), posterior cortical atrophy (PCA), corticobasal syndrome (CBS) and comportmental disorder (frontotemporal dementia behavioral variant (bvFTD)). For some of these focal non-amnestic syndromes, in particular CBS and PPA, it may be hard to reliably predict on clinical grounds what the underlying neuropathology will be, Alzheimer's disease or FTLD [47]. Detailed neurolinguistic phenotyping allows to estimate the probability of AD as an underlying cause of PPA but requires neurolinguistic expertise [48], in particular at the initial stages of the diseaes [49*].

6.3 High cerebrovascular load on MRI

In an amyloid imaging study of subcortical vascular disease, approximately one third of cases were ^{11}C-PIB positive [50]. The amount of white matter hyperintensities correlates with ^{11}C-PIB based measures of Aβ load in

patients with clinically probable cerebral amyloid angiopathy (CAA) but not in AD [51]. Based on the amyloid scan it may be impossible to distinguish between CAA and AD [52].

6.4 Clinical diagnosis of probable or possible Lewy body disease

In an amyloid imaging study, 11 out of 13 clinically probable Lewy body dementia (DLBD) patients had a positive ^{11}C-PIB scan [53], compared to only 2 out of 12 patients with Parkinson's disease with dementia. This has been confirmed by other studies using ^{18}F-ligands [12]. Therefore, usefulness in DLBD is probably limited since a number of cases have a positive amyloid scan despite the absence of neuritic plaques [23**].

6.5 Prediction in MCI

A positive amyloid scan in a patient with mild cognitive impairment (MCI) has predictive value for future cognitive decline with a 5-year conversion sensitivity of 85-93% and specificity between 81-100% [16**, 41, 38*, 21*]. In Alzheimer's Disease Neuroimaging Initiative (ADNI), the prevalence of a positive amyloid scan in early MCI patients is 43% and in late MCI patients 62% [41]. As long as there is no proven therapy in the predementia stage of AD, the diagnosis of amyloid-positivity in a case with MCI will prolong the phase during which a subject has to live with a diagnosis of prodromal AD/MCI due to AD. The time course of decline is currently hard to predict at the individual level. The effect of disclosing a positive or negative amyloid scan result in MCI patients in clinical practice is an important topic for future research.

6.6 Healthy controls

In AD mutation carriers, a gradual increase in amyloid ligand retention occurs years before clinical symptoms according to cross-sectional studies [54**, 55**]. Indirect evidence suggests that it may take approximately 15 years to evolve from a clearly negative amyloid scan to a plateau level [56**]. The amyloid increase probably continues into the MCI stage to level off prior to the dementia stage [57].

With our current knowledge we are not able to reliably predict on the basis of the amyloid scan alone at the individual level which cognitively intact individual will deteriorate cognitively or when [30**]. Due to this uncertainty and also given the absence of any proven intervention to ward off future decline, amyloid scanning is not indicated outside a research context in healthy volunteers [20**, 58*].

6.7 Summary

Based on the above considerations, we discern 4 situations where amyloid PET as biomarker evidence may contribute to the differential diagnostic process in a way that is relevant for the patient and the caregivers concerned [59*] (Fig. 3):

1. Early-onset dementia (onset before 60 years of age), in the absence of a known genetic mutation in the family
2. Focal cortical syndromes: PPA and CBS
3. The presence of comorbidity that could explain the cognitive decline, i.e. high vascular load on structural MRI, long-standing psychiatric history, medical comorbidity.
4. Rapidly progressive cognitive deterioration

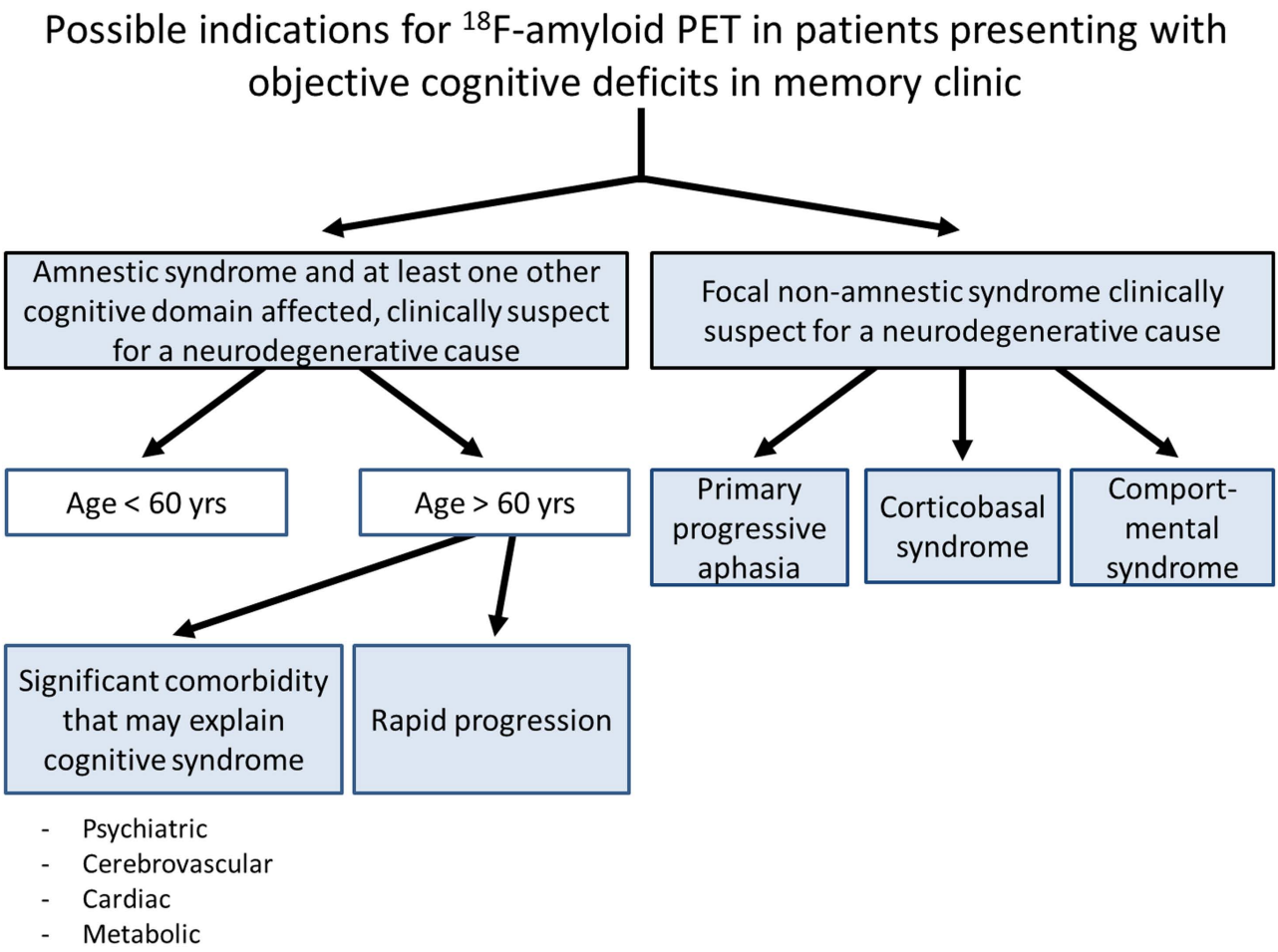

Figure 3: **Clinical utility of amyloid imaging.** Proposed clinical algorithm for the utility of amyloid imaging in patients presenting at a memory clinic with a cognitive deficit that is confirmed by clinical assessment of cognitive functions or by neuropsychological evaluation. This algorithm is tentative and subject to further empirical evaluation.

7 Conclusion

Currently the validity of amyloid PET for detecting the presence of moderate to severe amounts of neuritic and diffuse plaques appears to be convincingly demonstrated, also for the new ^{18}F-ligands. Studies of clinical utility however are only emerging. Among the most critical questions for near future empirical research in this context are the benefit of disclosure of a positive or negative amyloid scan in MCI patients in clinical practice, the comparison of clinical utility between amyloid PET and CSF AD biomarker analysis, and the efficacy of amyloid imaging in terms of patient outcome.

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9 Bullet points

1. Amyloid PET is a valid biomarker for neuritic amyloid plaque load, although cases with abundant diffuse plaques and scant neuritic plaques may also be positive.
2. Recent clinicopathological studies concur with in vivo amyloid imaging in demonstrating that there is room for improvement in accuracy in expert centres for diagnosing Alzheimer's disease in the initial years of the disease course.
3. Current algorithms take a restrictive approach to the use of amyloid imaging and delineate specific circumstances where amyloid imaging is indicated.

References

[1] Hyman BT, Phelps CH, Beach TG, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. *Alzheimers Dement*, 2012, 8:1–13.

[2] Mirra SS, Heyman A, McKeel D, et al. The Consortium to Establish a Registry of Alzheimer's Disease. II. Standardization of the neuropathologic assessment of Alzheimer's Disease. *Neurology*, 1991, 41:479–486.

[3] Thal DR, Rüb U, Orantes M, Braak H. Phases of a beta-deposition in the human brain and its relevance for the development of AD. *Neurology*, 2002, 58:1791–1800.

[4] Braak H and Braak E. Neuropathological stageing of Alzheimer-related changes. *Acta neuropathologica*, 1991, 82:239–259.

[5] ** Beach TG, Monsell SE, Phillips LE, and Kukull W. Accuracy of the clinical diagnosis of Alzheimer disease at National Institute on Aging Alzheimer disease centers, 2005-2010. *J Neuropathol Exp Neurol*, 2012, 71:266–273.
This recent prospective clinicopathological study is particularly valuable given the emphasis on limiting the selection bias for brain donation within the participating Alzheimer Disease Centers. It includes 919 cases diagnosed at National Institute of Aging (NIA) Alzheimer's Disease Centres (592 clinically probable AD cases, 122 clinically possible AD cases and 271 with non-AD dementia) and evaluates the accuracy of a clinical diagnosis of probable and possible AD as well as non-AD dementia against a neuropathological standard of truth.

[6] ** Ni R, Gillberg PG, Bergfors A, et al. Amyloid tracers detect multiple binding sites in Alzheimer's disease brain tissue. *Brain*, 2013, 136:2217–2227.
This study enhances our insight into the details of binding of amyloid ligands to amyloid aggregates, which is highly valuable. This displacement study used homogenized brain tissue from 23 AD patients and 20 controls comparing BTA-1, florbetapir, florbetaben, NAV4694, and FDDNP.

[7] Wolk DA, Zhang Z, Boudhar S, et al. Amyloid imaging in Alzheimer's disease: comparison of florbetapir and Pittsburgh compound-B positron emission tomography. *J Neurol Neurosurg Psychiatry*, 2012, 83:923–926.

[8] Landau SM, Breault C, Joshi AD, et al. Amyloid-β imaging with Pittsburgh compound B and florbetapir: comparing radiotracers and quantification methods. *J Nucl Med*, 2013, 54:70–77.

[9] ** Rowe CC, Pejoska, Mulligan RS, et al. Head-to-head comparison of 11C-PIB and 18F-AZD4694

(NAV4694) for β-amyloid imaging in aging and dementia. *J Nucl Med*, 2013, 54:880–886.
Twenty-five healthy elderly controls, 10 subjects with MCI, 7 subjects with probable AD and 3 subjects with FTLD participated in this comparative study between ^{11}C-PIB and ^{18}F-AZD4694. ^{18}F-AZD4694 is the first ^{18}F-labelled amyloid ligand to also show a high correlation with ^{11}C-PIB in white matter.

[10] Vandenberghe R, Van Laere K, Ivanoiu A, et al. 18F-flutemetamol amyloid imaging in Alzheimer disease and mild cognitive impairment: a phase 2 trial. *Ann Neurol*, 2010, 68:319–329.

[11] Joshi AD, Pontecorvo MJ, Clark CM, et al. Performance characteristics of amyloid PET with florbetapir F18 in patients with Alzheimer's disease and cognitively normal subjects. *J Nucl Med*, 2012, 53:378–384.

[12] Villemagne VL, Ong K, Mulligan RS, et al. Amyloid imaging with (18)F-florbetaben in Alzheimer disease and other dementias. *J Nucl Med*, 2011, 52:1210–1217.

[13] Cselényi Z, Jönhagen ME, Forsberg A, et al. Clinical validation of 18F-AZD4694, an amyloid-β-specific PET radioligand. *J Nucl Med*, 2012, 53:415–424.

[14] ** Rinne JO, Wong DF, Wolk DA, et al. [(18)F]flutemetamol PET imaging and cortical biopsy histopathology for fibrillar amyloid β detection in living subjects with normal pressure hydrocephalus: pooled analysis of four studies. *Acta Neuropathol*, 2012, 124:833–845.
This is a pooled analysis of a total of 52 scans performed over 4 sites: in two studies (n $=$ 22), biopsy had been performed well before the ^{18}F-flutemetamol scan. In two other studies (n $=$ 30), the ^{18}F-flutemetamol scan was done prior to shunt procedure and biopsy, allowing a direct topographical correspondence between the regional SUVR measure and the neuropathological findings. The primary outcome consisted of a regression analysis between regional SUVR and 4G8 immunostaining surface area in the region to be biopsied or the region surrounding the biopsy area. The correlation coefficient was 0.414. Correspondence was far from systematic: The subject with the highest amyloid area (14% of amyloid) had a SUVR of only 1.6 at the site of biopsy and the subjects with highest SUVR ($=$ 3) had rather low amyloid area ($=$ 2.4%).

[15] Ng S, Villemagne VL, Berlangieri S, et al. Visual assessment versus quantitative assessment of 11C-PIB PET and 18F-FDG PET for detection of Alzheimer's disease. *J Nucl Med*, 2007, 48:547–552.

[16] ** Doraiswamy PM, Sperling RA, Coleman RE, et al. Amyloid-β assessed by florbetapir F18 PET and 18-month cognitive decline: a multicenter study. *Neurology*, 2012, 79:1636–1644.
In the phase 2 ^{18}F-florbetapir study, 51 MCI patients participated along with 69 healthy controls and 31 AD patients. 37% of the MCI patients were amyloid positive. Forty-six of the patients were followed for 18 months. This is one of the few studies that explicitly mentions blinding of the evaluator. Of the amyloid positive MCI subjects (n $=$ 17) 5 progressed in an 18-months follow-up period. Of those who were amyloid negative (n $=$ 29), 3 progressed.

[17] Barthel H, Gertz HJ, Dresel S, et al. Cerebral amyloid-β PET with florbetaben (18F) in patients with Alzheimer's disease and healthy controls: a multicentre phase 2 diagnostic study. *Lancet Neurol*, 2012, 10:424–435.

[18] Tiepolt S, Barthel H, Butzke D, et al. Influence of scan duration on the accuracy of β-amyloid PET with florbetaben in patients with Alzheimer's disease and healthy volunteers. *Eur J Nucl Med Mol Imaging*, 2013, 40:238–244.

[19] Villemagne VL, Mulligan RS, Pejoska S, et al. Comparison of 11C-PIB and 18F-Forbetaben for aβ imaging

in ageing and Alzheimer's disease. *Eur J Nucl Med Mol Imaging*, 2012, 39:983–989.

[20] ** Johnson KA, Minoshima S, Bohnen NI, et al. Appropriate use criteria for amyloid PET: a report of the amyloid imaging task force, the society of nuclear medicine and molecular imaging, and the Alzheimer's Association. *Alzheimers Dement*, 2013, 9:e–1–16.
The Alzheimer's Association and the Society for Nuclear Medicine convened a taskforce of dementia and amyloid imaging experts to formulate what they judged to be appropriate and, as importantly, inappropriate use of amyloid imaging. The appropriate use criteria are discussed in the main text. Among the conditions where amyloid imaging is inappropriate, the authors listed patients with core clinical criteria for probable AD, patients with a cognitive complaint that is unconfirmed on clinical examination, asymptomatic individuals and for nonmedical use (e.g., legal, insurance coverage, or employment screening).

[21] * Vandenberghe R, Nelissen N, Salmon E, et al. Binary classification of (18)F-flutemetamol PET using machine learning: Comparison with visual reads and structural MRI. *Neuroimage*, 2012, 64C:517–525.
The authors used a classical supervised machine learning approach to compare the discriminative value of 18F-flutemetamol PET and MRI gray matter maps to discriminate between clinically probable AD, MCI and normal controls. In this manner, diagnostic performance of different imaging techniques can be determined within a same mathematical framework in an unbiased manner.

[22] ** Clark CM, Pontecorvo MJ, Beach TG, et al. Cerebral PET with florbetapir compared with neuropathology at autopsy for detection of neuritic amyloid-β plaques: a prospective cohort study. *Lancet Neurol*, 2012, 11:669–678.
In the industry-sponsored phase 3 trial of ^{18}F-florbetapir, subjects with a life expectancy of less than 6 months at enrollment, aged between 49 and 103 years (mean 79 years), underwent a florbetapir scan and donated their brains following demise. The primary outcome was based on a binarized CERAD neuritic plaque count, a binary score which had been newly developed for this type of study. Out of 59 cases, 39 had a moderate to high neuritic plaque density. Of these, 36 had a positive florbetapir scan. No false-positives were encountered.

[23] ** Kantarci K, Yang C, Schneider JA, et al. Antemortem amyloid imaging and β-amyloid pathology in a case with dementia with Lewy bodies. *Neurobiol Aging*, 2012, 33:878–885.
This is a thorough clinicopathological case study encompassing both conventional diagnostic procedures and quantitative immunohistochemical analysis. ^{11}C-PIB retention correlated with Aβ density (10D5 antibody), and not with NFT or with Lewy body density. A positive ^{11}C-PIB scan does not equate the presence of moderate to severe amount of neuritic plaques as it can also occur when diffuse plaques are abundant and neuritic plaques are sparse.

[24] * Driscoll I, Troncoso JC, Rudow G, et al. Correspondence between in vivo (11)C-PIB PET amyloid imaging and postmortem, region-matched assessment of plaques. *Acta Neuropathol*, 2012, 124:823–831.
In the Baltimore Longitudinal Study of Aging (BLSA), a community-recruited cohort is followed longitudinally with cognitive assessments until close to time of death and brain autopsy. A first series of autopsied cases is reported who received a ^{11}C-PIB scan.

[25] ** Ikonomovic MD, Abrahamson EE, Price JC, et al. Early AD pathology in a [C-11]PIB-negative case: a PIB-amyloid imaging, biochemical, and immunohistochemical study. *Acta Neuropathol*, 2012, 123:433–447.
In this case study, a case with Lewy body disease and a negative ^{11}C-PIB scan had focal deposition of abundant neuritic plaques limited to only one of the CERAD predefined regions (prefrontal cortex). ^{11}C-

PIB retention values correlate with Enzyme Linked ImmunoSorbent Assay (ELISA) measurements of Aβ42 more so than Aβ40.

[26] Schöll M, Wall A, Thordardottir S, et al. Low PIB PET retention in presence of pathologic CSF biomarkers in arctic app mutation carriers. *Neurology*, 2012, 79:229–236.

[27] Thurfjell L, Lötjönenand J, Koikkalainen R, et al. Combination of biomarkers: PET ^{18}F-flutemetamol imaging and structural MRI in dementia and mild cognitive impairment. *Neurodegenerative Dis*, 2012, 10:246-249.

[28] ** Duara R, Loewenstein DA, Shen Q, et al. Amyloid positron emission tomography with (18)F-flutemetamol and structural magnetic resonance imaging in the classification of mild cognitive impairment and Alzheimer's disease. *Alzheimers Dement*, 2013, 9:295–301.
On the basis of the phase 2 ^{18}F-flutemetamol phase 2 data, the authors demonstrate a significant degree of discordance between visual assessments of medial temporal atrophy and amyloid-positivity in MCI and in elderly controls. Medial temporal atrophy is more frequent than amyloid-positivity in these two groups.

[29] ** Jack CR Jr, Knopman DS, Weigand SD, et al. An operational approach to National Institute on Aging-Alzheimer's association criteria for preclinical Alzheimer disease. *Ann Neurol*, 2012, 71:765–775.
Until 2012 nearly all series of amyloid imaging in cognitively intact subjects were convenience samples from community-recruited subjects. Recently, a series of papers have appeared that are population-based, principally from the Mayo Clinic Study of Aging (MSCA), consisting of 430 subjects who received MRI, amyloid PET and neuropsychological assessment (mean age 78 years).

[30] ** Knopman DS, Jack CR Jr, Wiste HJ, et al. Brain injury biomarkers are not dependent on β-amyloid in normal elderly. *Ann Neurol*, 2013, 73:472480.
This study was among the first to directly test a novel National Institute of Aging-Alzheimer Association (NIA-AA) classification of imaging findings in cognitively intact older adults. The NIA-AA classification was based on one of the prevailing models of the time course of AD biomarker changes. The current study highlights the relatively frequent occurrence of a separate, unpredicted class of cases with AD-like changes on MRI or FDG-PET in the absence of increased amyloid load (coined 'SNAP'). This questions one of the prevailing heuristic models of the sequence of AD biomarker change.

[31] Furst AJ, Rabinovici GD, Rostomian AH, et al. Cognition, glucose metabolism and amyloid burden in Alzheimer's disease. *Neurobiol Aging*, 2012, 33:215–225.

[32] * Lehmann M, Ghosh PM, Madison C, et al. Diverging patterns of amyloid deposition and hypometabolism in clinical variants of probable Alzheimer's disease. *Brain*, 2013, 136:844–858.
Alzheimer's disease syndromes are associated with degeneration of specific functional networks, and fibrillar amyloid-β deposition explains at most a small amount of the clinico-anatomic heterogeneity in Alzheimer's disease.

[33] ** Gefen T, Gasho K, Rademaker A, et al. Clinically concordant variations of Alzheimer pathology in aphasic versus amnestic dementia. *Brain*, 2012, 135:1554–1565.
This clinicopathological stereological study tests and confirms the hypothesis that when AD presents with a primary progressive aphasia phenotype, this atypical presentation reflects the unusual topography of neurofibrillary tangles. The phenotype is unrelated to the topography of neuritic plaques.

[34] Devanand DP, Mikhno A, Pelton GH, et al. Pittsburgh compound B (11C-PIB) and fluorodeoxyglucose (18F-FDG) PET in patients with Alzheimer disease, mild cognitive impairment, and healthy controls. *J Geriatr Psychiatry Neurol*, 23(3):185–198, Sep 2010.

[35] Rabinovici GD, Rosen HJ, Alkalay A, et al. Amyloid vs FDG-PET in the differential diagnosis of AD and FTLD. *Neurology*, 2011, 77:2034–2042.

[36] Fagan AM, Mintun MA, Shah AR, et al. Cerebrospinal fluid tau and ptau(181) increase with cortical amyloid deposition in cognitively normal individuals: implications for future clinical trials of Alzheimer's disease. *EMBO Mol Med*, 2009, 1:371–380.

[37] Landau SM, Lu M, Joshi AD, et al. Comparing PET imaging and CSF measurements of aβ. *Ann Neurol*, 2013, Mar.

[38] * Nordberg A, Carter SF, Rinne J, et al. A european multicentre PET study of fibrillar amyloid in Alzheimer's disease. *Eur J Nucl Med Mol Imaging*, 2013, 40:104–114.
This is a pooled analysis of 238 scans collected at 5 different European centres (97 AD, 72 MCI, 51 healthy controls). The distribution of retention values for the different patient groups was comparable between centres.

[39] ** Ossenkoppele R, Prins ND, Pijnenburg YAL, et al. Impact of molecular imaging on the diagnostic process in a memory clinic. *Alzheimers Dement*, 2013, 9:414-21.
This prospective investigator-driven study included 154 patients from an academic memory clinic (average age 64 years, MMSE scores mainly above 20 out of 30). As an inclusion criterion for the main group of cases, diagnostic confidence prior to inclusion had to be lower than 90%. In addition to the standard diagnostic work-up, the patients received for research purposes a paired ^{11}C-PIB and FDG-PET. Sixty-one % of patients who had received a clinical diagnosis of AD in an academic memory clinic had a positive ^{11}C-PIB scan, 28% of patients with a clinical diagnosis of FTD, 80% of patients with LBD and 30% of patients with other dementias.

[40] * Grundman M, Pontecorvo MJ, Salloway SP, et al. Potential impact of amyloid imaging on diagnosis and intended management in patients with progressive cognitive decline. *Alzheimer Dis Assoc Disord*, 2013, 27:4–15.
Amyloid imaging results altered physician's diagnostic thinking, intended testing, and management of patients undergoing evaluation for cognitive decline.

[41] Landau SM, Mintun MA, Joshi AD, et al. Amyloid deposition, hypometabolism, and longitudinal cognitive decline. *Ann Neurol*, 2012, 72:578–586.

[42] Schipke CG, Peters O, Heuser I, et al. Impact of beta-amyloid-specific florbetaben PET imaging on confidence in early diagnosis of Alzheimer's disease. *Dement Geriatr Cogn Disord*, 2012, 33:416–422.

[43] * Mathis CA, Kuller LH, Klunk WE, et al. In vivo assessment of amyloid-β deposition in nondemented very elderly subjects. *Ann Neurol*, 2012, Nov.
Subjects above 80 years of age represent a significant and increasing proportion of patients in clinical practice but are commonly underrepresented in clinical studies. This study, which is based on a subgroup of participants of the Gingko Evaluation of Memory Study, provides an estimate of the prevalence of a positive amyloid scan in cognitively normal (51% amyloid-positive) and MCI (68% amyloid-positive) subjects with a mean age of 85, the youngest being 82 years.

[44] Mesulam MM. Behavioral neuroanatomy: Large-scale networks, association cortex, frontal syndromes, the limbic system and hemispheric specializations (pages 1-120). Aging, Alzheimer's disease and dementia: Clinical and neurobiological perspectives (pages 439-522). In M.M. Mesulam, editor, *Principles of behavioral and cognitive neurology*, 2000. Oxford University Press, New York, NY.

[45] ** Hornberger M, Wong S, Tan R, et al. In vivo and post-mortem memory circuit integrity in frontotemporal dementia and Alzheimer's disease. *Brain*, 2012, 135:3015–3025.
This study thoroughly examines the amnestic syndrome that can occur early in FTLD and compares its features and neuroanatomical basis with that seen in AD. It is an important study for clinicians as it reinforces the idea that FTLD can present initially in ways that are hardly distinguishable from the amnestic syndrome typically seen in AD.

[46] ** Snitz BE, Weissfeld LA, Lopez OL, et al. Cognitive trajectories associated with β-amyloid deposition in the oldest-old without dementia. *Neurology*, 2013, 80:1378–1384.
This important study provides evidence for the relevance of amyloid-positivity as one of the determinants of cognitive change during aging. In a subgroup of the GEMS study (total sample size $= 194$), the cognitive trajectories were reconstructed over the 7-9 years preceding the amyloid scan. Cognitive decline was more pronounced in the amyloid-positive group.

[47] Alladi S, Xuereb J, Bak T, et al. Focal cortical presentations of Alzheimer's disease. *Brain*, 2007, 130:2636–2645.

[48] Leyton CE, Villemagne VL, Savage S. Subtypes of progressive aphasia: application of the international consensus criteria and validation using β-amyloid imaging. *Brain*, 2011, 134:3030–3043.

[49] * Mesulam MM, Wieneke C, Thompson C. Quantitative classification of primary progressive aphasia at early and mild impairment stages. *Brain*, 2012, 135:1537–1553.
Strict application of the Gorno-Tempini et al. (2011) core and ancillary guidelines, through the uniform administration of standardized tests and explicit cut-off scores, led to the classification of 80% of patients at the mild and early disease stages. The inclusion of a mixed phenotype into the list of variants raises the success rate to nearly 90%.

[50] Lee JH, Kim SH, Kim GH, et al. Identification of pure subcortical vascular dementia using 11C-Pittsburgh compound B. *Neurology*, 2011, 77:18–25.

[51] Gurol ME, Viswanathan A, Gidicsin C, et al. Cerebral amyloid angiopathy burden associated with leukoaraiosis: A positron emission tomography/magnetic resonance imaging study. *Ann Neurol*, 2012, Dec.

[52] Dhollander I, Nelissen N, Van Laere K, et al. In vivo amyloid imaging in cortical superficial siderosis. *J Neurol Neurosurg Psychiatry*, 2011, 82:469–471.

[53] Edison P, Rowe CC, Rinne JO, et al. Amyloid load in Parkinson's disease dementia and Lewy body dementia measured with [11C]PIB positron emission tomography. *J Neurol Neurosurg Psychiatry*, 2008, 79:1331–1338.

[54] ** Fleisher AS, Chen K, Quiroz YT, et al. Florbetapir PET analysis of amyloid-β deposition in the presenilin 1 E280A autosomal dominant Alzheimer's disease kindred: a cross-sectional study. *Lancet Neurol*, 2012, 11:1057–1065.
In the Alzheimer Prevention Initiative study, 11 symptomatic presenilin 1 E280A mutation carriers, 19 presymptomatic mutation carriers and 20 asymptomatic noncarriers received an ^{18}F-florbetapir scan cross-

sectionally. Increase in PET signal was seen more than 15 years prior to predicted symptom onset. The phase during which the signal increased until it reached plateau had a duration of about 9 years. This study provides direct and fundamental insight into the timecourse of amyloid accumulation, although the findings will need to be confirmed by longitudinal studies in this population and should not be necessarily extrapolated to sporadic AD.

[55] ** Bateman RJ, Xiong C, Benzinger TLS, et al. *N Engl J Med*, 2012, 367:795–804.
The Dominantly Inherited Alzheimer Network is a prospective longitudinal study in AD mutation carriers. This report is based on cross-sectional data in 128 carriers of AD mutations. Changes in amyloid load were observed more than 15 years before the predicted age of symptom onset.

[56] ** Jack CR Jr, Wiste HJ, Lesnick TG, et al. Brain β-amyloid load approaches a plateau. *Neurology*, 2013, 80:890–896.
According to a longitudinal amyloid imaging study in 260 cases with repeat amyloid scans with an average 1.3 years interval, 200 of whom were cognitively intact, the annual rate of Aβ increase is strongly dependent on baseline SUVR: it is highest for a baseline SUVR$_{comp}$ around 2. By integrating the curve that plots rate of increase against baseline SUVR, the duration can be mathematically inferred that it would take to evolve from a strictly negative amyloid scan to an asymptotic plateau level.

[57] Jack CR Jr, Knopman DS, Jagust WJ, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. *Lancet Neurol*, 2013, 12:207–216.

[58] * Chételat G, La Joie R, Villain N, et al. Amyloid imaging in cognitively normal individuals, at-risk populations and preclinical Alzheimer's disease. *NeuroImage: Clinical*, 2013, 2:356365
This review focuses on issues related to amyloid positive scans in healthy controls, dealing with prevalence, risk factors, cognitive effects, predictive value and ethics.

[59] * Vandenberghe R, Adamczuk K, Dupont P, et al. Amyloid PET in clinical practice: Its place in the multidimensional space of Alzheimer's disease. *NeuroImage: Clinical*, 2013, 2:497-511
This review proposes a multidimensional model of Alzheimer's disease and suggests potential indications for amyloid imaging in clinical research and practice.